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Review article

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Metformin in gestational diabetes: physiological actions and clinical applications

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Abstract

Metformin is an effective oral hypoglycaemic agent used in the treatment of type 2 diabetes mellitus; however, its use in pregnancy for the treatment of gestational diabetes mellitus (GDM) remains controversial owing to concerns around safety and efficacy. This comprehensive review outlines the physiological metabolic functions of metformin and synthesizes existing literature and key knowledge gaps pertaining to the use of metformin in pregnancy across various end points in women with GDM. On the basis of current evidence, metformin reduces gestational weight gain, neonatal hypoglycaemia and macrosomia and increases insulin sensitivity. However, considerable heterogeneity between existing studies and the grouping of aggregate and often inharmonious data within meta-analyses has led to disparate findings regarding the efficacy of metformin in treating hyperglycaemia in GDM. Innovative analytical approaches with stratification by individual-level characteristics (for example, obesity, ethnicity, GDM severity and so on) and treatment regimens (diagnostic criteria, treatment timing and follow-up duration) are needed to establish efficacy across a range of end points and to identify which, if any, subgroups might benefit from metformin treatment during pregnancy.

Sections

Introduction

Complex physiological actions of metformin

Metformin safety profile in pregnancy

Metformin efficacy in GDM

Limitations and future directions

Conclusions

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Key points

- The use of metformin for the management of gestational diabetes mellitus (GDM) is highly contested, with divergent clinical recommendations between countries.
- Metformin has a broad spectrum of physiological actions beyond its known glucoregulatory and insulin-sensitizing properties, suggesting potential clinical benefits for GDM.
- Despite a well-established safety profile in pregnancy, transplacental passage of metformin raises concerns regarding the long-term metabolic health of offspring, for which no definitive data currently exist.
- Metformin seems to be effective for reducing gestational weight gain, neonatal hypoglycaemia and macrosomia, but its efficacy for glycaemic control in GDM has not been demonstrated.
- Considerable heterogeneity exists between studies, particularly in individual-level characteristics (for example, obesity, ethnicity, GDM severity and so on) and treatment regimens (diagnostic criteria, treatment timing, targets and durations).
- Analysis of individual participant data from randomized controlled trials with long-term follow-up will be a critical next step to address the unanswered questions regarding metformin use in pregnancy.

Introduction

Diabetes is a metabolic disorder arising from defective insulin secretion, insulin action or both, resulting in high blood glucose concentrations[1]. An ageing population, coupled with sedentary lifestyles and overconsumption of energy-dense foods, has contributed to a rise in global obesity and the rapid propagation of diabetes and related comorbidities[2]. Concurrently, the prevalence of obesity and diabetes in pregnancy has become a worldwide health problem, although the effect of these metabolic disorders on pregnancy outcomes is not well understood.

Diabetes during pregnancy can be classified as pre-existing type 1 or type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM), all of which, if not properly managed, can contribute to adverse maternal and neonatal outcomes. Type 1 diabetes mellitus is an autoimmune condition usually occurring in children and young adults that arises from the destruction of pancreatic β-cells. This leads to absolute insulin deficiency and hyperglycaemia, necessitating insulin-replacement therapy[3]. By contrast, T2DM often occurs in adults in association with lifestyle risk factors (such as obesity) and genetics and is characterized by the non-autoimmune development of a functional deficit in insulin production and/or sensitivity, with impaired glucose tolerance. Depending on the severity and progression of the disease, lifestyle changes, oral medications (such as metformin) and insulin administration are viable treatment options[3].

With a similar pathophysiology to T2DM, GDM refers to clinical hyperglycaemia with onset during pregnancy and resolution after delivery, and is one of the most common pregnancy complications[4]. In 2012, the global prevalence of GDM was estimated to range from 1% to 28% depending on diagnostic criteria and screening strategies, which vary considerably by region[5] (Table 1). More recent global estimates from 1990 to 2020 suggest that the pooled global standardized prevalence of GDM is 14%, with considerable variation by region[6] (Fig. 1). With its rising prevalence, the pathogenesis of GDM and its long-term outcomes requires greater research focus.

GDM is considered an important risk factor for pregnancy complications including preeclampsia, macrosomia and neonatal hypoglycaemia, as well as maternal T2DM and cardiovascular diseases later in life[4]. Infants born to mothers with GDM might be at an increased risk of developing obesity and diabetes in adulthood[4]. Given its effect on immediate-term and long-term health outcomes, effective strategies to adequately treat GDM are paramount for mitigating its consequences for both mother and child. Beyond its physical health risks, the high prevalence of GDM also has an economic effect on health systems globally. Costs are increased by the additional antenatal care required for managing GDM and its complications during pregnancy and postpartum[5]. These costs include diabetes education sessions, dietetic appointments, secondary growth scans, follow-up testing and medication costs[7,8].

In this Review, we first explore the complex actions of metformin in metabolic regulation, providing a plausible basis for its potential benefits in the management of GDM. Second, we evaluate the safety profile of metformin use during pregnancy and critically assess the evidence for and against its use in patients with GDM, drawing on evidence from epidemiological studies, randomized controlled trials (RCTs) and meta-analyses. Finally, we highlight the major limitations in the literature, outlining the key considerations and analytical approaches needed for advancing this field of research.

Complex physiological actions of metformin

Metformin, derived from galegine (obtained from the plant *Galega officinalis*)[9], is a first-line therapy in the treatment of T2DM[10]. Metformin has been extensively evaluated for its pharmacokinetic properties in healthy individuals as well as in patients with diabetes[11]. The half-life of metformin is ~5–6 h and it is not bound to plasma proteins or metabolized in the liver, but is excreted unchanged in the urine[12–14]. Thus, in patients with renal insufficiency, metformin accumulates in the kidneys resulting in an increased risk of lactic acidosis, although this is a very rare occurrence[15] with an estimated incidence of 0.03–0.05 cases per 1,000 person-years[16].

Metformin promotes a reduction in hepatic glucose production by increasing the insulin sensitivity of tissues, reducing intestinal glucose absorption and improving peripheral glucose uptake and utilization. These actions maintain blood glucose at normal levels without causing hypoglycaemic episodes or increased body weight — common sequelae associated with insulin use[17]. At a cellular level, the physiological actions of metformin are thought to occur via activation of a key regulator of cellular energy status, the 5′ adenosine monophosphate-activated protein kinase (AMPK) signalling pathway[18,19], although effects independent to this pathway have also been suggested[20], as described subsequently (Fig. 2). These actions of metformin are potentially useful during pregnancy in which physiological adaptations can lead to deteriorations in glucose control, with alterations in preprandial and postprandial glucose metabolism and ensuing insulin resistance.

Cellular energy regulation

Metformin induces mild inhibition of mitochondrial respiratory chain complex I. This increases cellular redox potential (that is, the ratio of reduced-to-oxidized NADH:NAD^+) and reduces ATP production, with a

Table 1 | Diagnostic criteria for gestational diabetes mellitus across institutions and world regions

Organization	Glucose load (g)	Fasting glucose, mmol/l (mg/dl)	1-h glucose, mmol/l (mg/dl)	2-h (±3 h) glucose, mmol/l (mg/dl)	Positive tests required	Country or region
ACOG[172a]	100	≥5.3 (≥95)	≥10.0 (≥180)	≥8.6 (≥155) 3-h: ≥7.8 (≥140)	2	North America
ADA, 2023 (ref. 3)[a]	75	>5.1 (>92)	>10.0 (>180)	>8.5 (>153)	1	North America
ADIPS, 2014 (ref. 173)	75	≥5.1 (≥92)	≥10.0 (≥180)	≥8.5 (≥153)	1	Australasia
BSD, FEBRASGO, 2014 (ref. 174)[b]	75	≥5.3 (≥95)	≥10.0 (≥180)	≥8.6 (≥155)	1	South America
CC, 1982 (ref. 175)	100	≥5.3 (≥95)	≥10.0 (≥180)	≥8.6 (≥155) 3-h: ≥7.8 (≥140)	2	Europe, North America
CDA, 2013 (ref. 176)[a]	75	≥5.3 (≥95)	≥10.6 (≥190)	≥9.0 (≥162)	1	Canada
DIPSI, 2009 (ref. 177)	75	–	–	≥7.8 (≥140)[c]	–	India
EASD, 1996 (ref. 178)	75	≥6.0 (≥108)	–	≥9.0 (≥162)	1	Europe
IADPSG, 2010 (ref. 179)[a]	75	≥5.1 (≥92)	≥10.0 (≥180)	≥8.5 (≥153)	1	North America, Italy, Sweden, Germany
JDS, 2013 (ref. 180)[a]	50	≥5.1 (≥92)	≥10.0 (≥180)	≥8.5 (≥153)	2	Japan
NDDG, 1979 (ref. 181)[a]	100	≥5.8 (≥105)	≥10.6 (≥190)	≥9.2 (≥165) 3-h: ≥8.0 (≥145)	2	North America, India
NICE, 2015 (ref. 182)	75 g	≥5.6 (≥100)	–	≥7.8 (≥140)	1	UK
WHO, 2019 (ref. 183); FIGO, IDF, 2015 (ref. 184)	75 g	5.1–6.9 (92–125)	≥10.0 (≥180)	8.5–11.0 (153–199)	1	Global

ACOG, American Congress of Obstetricians and Gynecologists; ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; BSD, Brazilian Diabetes Society; FEBRASGO, Brazilian Federation of Gynecology and Obstetrics Societies; CC, Carpenter-Coustan; CDA, Canadian Diabetes Association; DIPSI, Diabetes in Pregnancy Study Group of India; EASD, European Association for the Study of Diabetes; FIGO, International Federation of Gynecology and Obstetrics; IDF, International Diabetes Federation; IADPSG, International Association of Diabetes and Pregnancy Study Group; JDS, Japan Diabetes Society; NDDG, National Diabetes Data Group; NICE, National Institute for health and Clinical Excellence. [a]May be preceded by a non-fasting 50 g glucose challenge and values >7.8 mmol/l (>140 mg/dl) proceed to oral glucose tolerance test as outlined (that is, two-step approach). [b]May be preceded by a fasting glucose test and values >4.7 mmol/l proceed to oral glucose tolerance test as outlined (that is, two-step approach). [c]Values are irrespective of meals before oral glucose challenge (that is, can be fasting or non-fasting).

concomitant increase in cellular AMP levels[9,21] ((1) in Fig. 2). Increased AMP levels inhibit the adenylate cyclase enzyme, reducing conversion of ATP to cAMP and dampening cAMP production upon stimulation of the glucagon receptor[21,22]. Reduced cAMP decreases protein kinase A activation, thereby increasing fructose-2,6-bisphosphate (F-2,6-BP). F-2,6-BP regulates conversion of F1,6BP to and from fructose-6-phosphate (F6P) via allosteric inhibition and activation of fructose-1,6-bisphosphatase (FBP1) and phosphofructokinase, respectively[23], enzymes that are critical in regulating the balance between glucose synthesis and breakdown. Specifically, phosphofructokinase catalyses the conversion of F6P to F-1,6-BP, promoting glycolysis (the key step in the glucose breakdown for energy), whereas FBP1 catalyses the conversion of F-1,6-BP to F6P, effectively reversing the glycolytic reaction to facilitate gluconeogenesis (synthesizing glucose from non-carbohydrate sources). By increasing F-2,6-BP and reducing gluconeogenic enzyme (FBP1) activity, gluconeogenesis is suppressed in response to metformin, whereas glycolysis is stimulated. Increased AMP:ATP ratio also enhances liver kinase B1-mediated activity of AMPK, with a plethora of downstream effects[24] ((2) in Fig. 2). One such effect is the phosphorylation and nuclear exclusion of transcription factors, including cAMP-response element binding protein (CREB) and foxhead box protein O1 (FOXO1) via CREB-regulated transcription co-activator 2 (refs. 25,26) (CRTC2). This is proposed to prevent the activation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, key regulators of gluconeogenic gene expression. As a result, conversion of oxaloacetate to phosphoenolpyruvate is diminished, decreasing the available substrate for gluconeogenesis[27].

Metformin is also thought to inhibit mitochondrial glycerol-3-phosphate dehydrogenase (mGDPH) directly in a redox-independent manner and indirectly via inhibiting mitochondrial respiratory chain complex IV[28] ((3) in Fig. 2). These actions reduce the activity of the glycerol–phosphate shuttle (by mGDPH and its cytosolic partner cGDPH, which transfers cytosolic NADH to mitochondria) and increase NADH:NAD^+ ratio. In turn, lactate dehydrogenase, which converts lactate to pyruvate in the cytosol, is inhibited[29]. The net result is a reduction in the availability of pyruvate from lactate and overall inhibition of gluconeogenesis.

Another novel pathway suggests that metformin, at low but clinically relevant doses, binds to presenilin enhancer 2, a subunit of the γ-secretase complex. This initiates a signalling route that intersects with the lysosomal glucose-sensing pathway via ATPase H^+ transporting accessory protein 1, a subunit of v-ATPase, leading to AMPK activation[30] ((4) in Fig. 2).

Insulin signalling and sensitivity

In skeletal muscle, AMPK activation by metformin promotes glucose transporter protein type 4 (GLUT4) translocation to the cell membrane, enhancing glucose uptake[31] ((5) in Fig. 2). This occurs via direct effects on TBC1 domain family member 1 (TBC1D1) and might also occur indirectly through modulation of insulin signalling, with

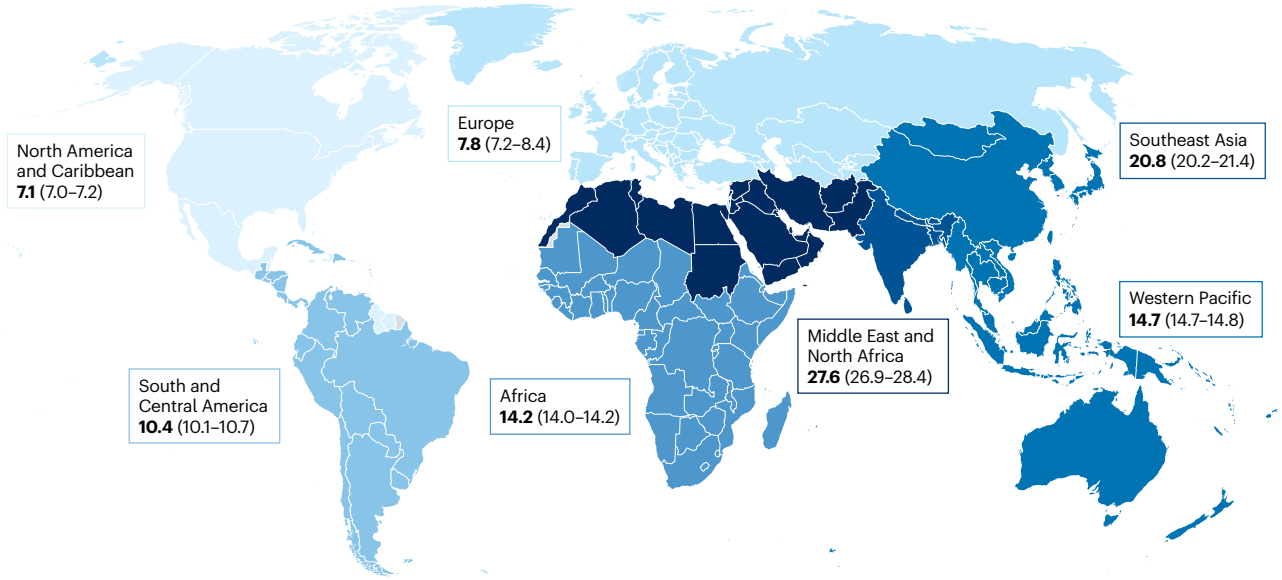

Fig. 1 | Standardized pooled prevalence of gestational diabetes mellitus by region, 1990–2020 inclusive. Country-specific estimate data from 1990 to 2020 were used to calculate pooled GDM prevalence and standardized by the International Association of Diabetes in Pregnancy Study Group diagnostic criteria, universal oral glucose tolerance test strategy and age (25–30 years), within each region[6].

activated Akt (protein kinase B) promoting GLUT4 translocation via TBC1D4 (refs. 32,33). Activated AMPK affects these complex Akt insulin signalling pathways to promote insulin sensitivity ((6) in Fig. 2). Under normal conditions, activated insulin or growth factor receptors trigger intrinsic tyrosine kinases, which in turn activate insulin receptor substrates (IRS) and subsequently Akt[34]. Upon AMPK activation by metformin, these substrates, namely, IRS1, are phosphorylated — a key regulatory step that dampens insulin or insulin growth factor 1 signalling and enhances insulin sensitivity. Phosphorylation of IRS1 reduces its ability to serve as a docking protein for downstream signalling molecules including class IA phosphatidylinositol-3 kinase, limiting the generation of phosphatidylinositol 3,4,5-triphosphate, a critical second messenger for recruiting and activating Akt[35]. Akt can itself modulate IRS1, providing a negative feedback loop that regulates the intensity and duration of insulin or insulin growth factor 1 signalling[36]. Diminished Akt affects multiple key downstream targets (such as CREB and FOXO1) including mechanistic target of rapamycin complex 1 (mTORC1) activity, a downstream effector that regulates protein synthesis and can also promote IRS1 phosphorylation under certain conditions (for example, high cellular energy or growth states)[35].

Gut–brain axis interactions

Metformin-activated AMPK inhibits mTORC1 via phosphorylation of tuberous sclerosis protein 2 (TSC2; also directly phosphorylated by Akt[37]) and the mTOR subunit Raptor, promoting autophagy and impacting various downstream cellular processes related to metabolism, growth and protein synthesis[38,39] ((7) in Fig. 2). Given that mTORC1 is a regulator of nutrient sensing, inhibition of this complex has indirect effects on gut hormones including an increase in glucagon-like peptide 1 (GLP1)[40]. GLP1 is an incretin hormone that regulates glucose homeostasis by promoting insulin secretion in pancreatic β-cells[41] and suppressing the secretion of glucagon, a peptide hormone that typically promotes hepatic glucose output[41,42]. GLP1 also inhibits the secretion of ghrelin, known as the 'hunger hormone'. This action might indirectly stimulate peptide tyrosine–tyrosine (PYY), a 'satiety hormone' that acts on receptors in the hypothalamus to decrease appetite and food intake and in the gut to slow down gastric emptying and intestinal transit time[41]. Indeed, ghrelin has been shown to supress PYY[43] and vice versa, with PYY suppressing ghrelin when infused in a fasted state among individuals with obesity and normal weight[44], supporting a reciprocal ghrelin–PYY regulatory mechanism. Collectively, these direct (insulin secretion and glucagon inhibition) and indirect (PYY–ghrelin regulation) mechanisms of mTORC1 and GLP1 contribute to overall regulation of blood glucose.

In addition to gut hormones, AMPK activation by metformin also induces the upregulation of gut antimicrobial peptides, mucin glycoproteins and bile acids, which, alongside inhibition of mTORC1 signalling[45], can modulate gut microbiota composition[21,29] ((8) in Fig. 2). This change in gut microbiota composition results in an increased abundance of beneficial species such as *Akkermansia*[46], *Bifidobacterium*[47] and *Lactobacillus*[48], while reducing potentially pathogenic species such as *Clostridium difficile*[49]. Such alterations in gut microbiota composition contribute to enhanced production of short-chain fatty acids such as acetate, butyrate and propionate via the fermentation of dietary fibres[47,50,51]. Short-chain fatty acids have pivotal roles in metabolic regulation by promoting lipolysis, modulating adipokine secretion, inhibiting inflammation and enhancing gut hormone production (including GLP1 and PYY)[52]. This cascade of events highlights the intricate interplay between AMPK signalling and the gut–brain axis to maintain the neural, hormonal and immune pathways involved in preserving metabolic homeostasis.

Lipid metabolism

AMPK inhibits de novo synthesis of fatty acids and lipogenesis and activates fatty acid uptake and β-oxidation via several mechanisms.

AMPK activation inhibits acetyl-CoA carboxylase through phosphorylation, reducing malonyl-CoA synthesis and subsequent fatty acid synthesis[53]. Simultaneously, inhibition of acetyl-CoA carboxylase relieves the inhibition of carnitine palmitoyltransferase 1, an enzyme involved in transporting fatty acids into mitochondria for oxidation, thereby promoting fatty acid oxidation[54] ((9) in Fig. 2). Translocation of fatty acid transporter CD36 to the plasma membrane by AMPK is also thought to increase fatty acid uptake and sequestration, although the exact mechanisms for this are unclear[55]. In adipocytes, AMPK inhibits lipogenesis via phosphorylation of SREBP1c Ser372 and suppression of SREBP1c-dependent lipogenic processes[56]. AMPK activation also regulates lipolysis through phosphorylation of the key enzymes, adipocyte triglyceride lipase and hormone-sensitive lipase[57,58] ((10) in Fig. 2). These processes impede hydrolysis of triglycerides stored in adipocytes into free fatty acids and glycerol and their subsequent release into the bloodstream. Glycerol can serve as a substrate for gluconeogenesis in the liver (via the glycerol–phosphate shuttle and increased levels of mitochondrial NADH)[59]; however, owing to the increased NADH:NAH$^+$ ratio induced by metformin (as described earlier), the phosphorylation of glycerol from white adipose tissue lipolysis to glycerol-3-phosphate is inhibited, as is subsequent conversion to dihydroxyacetone phosphate, a key gluconeogenic intermediate necessary for hepatic glucose production[59]. These AMPK-dependent and redox-dependent actions of metformin work in a complex manner to regulate lipid metabolism, preventing excess lipid accumulation and liver steatosis, while improving insulin sensitivity and glucose homeostasis to mitigate the cardiometabolic milieu of dyslipidaemia.

Inflammation and inflammasome modulation

AMPK activation inhibits nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signalling via several pathways. The primary mechanism is via inhibiting IκB kinase (IKK) and its phosphorylation and activation of the inhibitor of κB (IκB)[60] (11 in Fig. 2). Stable unphosphorylated IκB proteins bind to NF-κB dimers (such as p50–p65), preventing their translocation into the nucleus, such that they remain sequestered in the cytoplasm as inactive complexes unable to activate transcription of target genes involved in inflammation, immune responses and cell proliferation[61]. This prevention of NF-κB translocation results in reduced expression of pro-inflammatory cytokines, chemokines, adhesion molecules and other inflammatory mediators. In a similar fashion, AMPK can modulate Janus kinase phosphorylation directly or via other mechanisms (for example, via mTOR or tuberous sclerosis protein 2 (ref. 62)), inhibiting signal transducer and activator of transcription 3 (ref. 63) and disrupting Janus kinase–signal transducer and activator of transcription signalling pathways[64] that influence NF-κB activation[65]. Reduced inflammation via AMPK-dependent inhibition of the Jun N-terminal kinase–NF-κB signalling pathway[61] and the Jun N-terminal kinase signalling cascade during monocyte-to-macrophage differentiation has also been reported[66]. Finally, metformin inhibited NF-κB in lipopolysaccharide-treated AMPK-null fibroblasts and macrophages, suggesting an AMPK-independent mechanism of inhibition, potentially via regulation of reactive oxygen species (ROS)[67].

A novel AMPK–NF-κB-independent pathway by which metformin might dampen inflammation has also been proposed. Here, direct inhibition of complex I by metformin reduces mitochondrial ATP synthesis, thus reducing cytosolic release of mtDNA, a potent ligand for the nucleotide-binding and oligomerization domain-like receptor protein 3 (NLRP3) inflammasome[68,69] (12 in Fig. 2). This reduction in oxidized mtDNA can occur either directly or via a reduction in ROS generation[70,71]. Decreased NLRP3 inflammasome activation inhibits caspase-1 activation, decreasing proteolytic processing of pro-inflammatory cytokines IL-1β and IL-18 (ref. 72). This disrupts the differentiation and activation of immune cells (macrophages, T cells and B cells) and affects a cascade of downstream events, including deactivation of transcription factors such as NF-κB[73], decreased release of inflammatory cytokines and improved tissue repair and homeostasis[72]. Indeed, metformin reduces the recruitment of monocytes to the vascular wall and their differentiation into inflammatory macrophages, thus reducing the formation of atherosclerotic plaque[66]. Together, these functions of metformin prevent translocation and expression of inflammatory genes, downregulate inflammatory mediators and suppress inflammasome activity to promote broad immunomodulatory effects that are beneficial for overall metabolic and angiogenic function[66].

The broad spectra of physiological actions of metformin have generated substantial interest in the potential use of this drug in the treatment of various conditions underpinned by insulin resistance, dyslipidaemia and inflammation, including obesity, polycystic ovary syndrome (PCOS), cancers and cardiovascular diseases, among others[74]. Indeed, metabolic regulation by metformin, whether via AMPK activation or other pathways, could plausibly address many of the clinical features of GDM, including insulin resistance, hyperglycaemia, dysregulated lipids, fatty acids and adipokines, oxidative stress and inflammation (Fig. 3). However, the use of metformin in pregnancy for the treatment of GDM remains controversial, with ongoing concerns surrounding both efficacy and safety.

Metformin safety profile in pregnancy

The safety and efficacy of metformin seem to be superior to other oral antidiabetic preparations such as sulfonylureas, α-glucosidase inhibitors and glitazones, with minor, self-limiting gastrointestinal adverse effects and rare complications such as lactic acidosis[17,75]. Sulfonylureas, such as glyburide, are insulin secretagogues and are reported to be generally inferior to metformin in pregnancy (leading to increased gestational weight gain, macrosomia and neonatal hypoglycaemia)[76]. New agents including GLP1 agonists and sodium-glucose co-transporter 2 inhibitors are more potent than metformin, but are not used in pregnancy owing to potential adverse effects on offspring[77]. Metformin use has been associated with nausea, diarrhoea and dysgeusia[78], whereas long-term use is linked to a higher prevalence of vitamin B12 deficiency in some[79], but not all[80], studies. No other serious drug-related complications have been reported with the use of metformin[81].

Unlike insulin, however, metformin can freely transverse the placenta and enter fetal circulation, whereby the fetus has at least half[82], if not the same or higher[83], concentration of metformin as maternal plasma. Although transplacental passage occurs freely via organic cation transporters, assessing the level of metformin that reaches the fetus requires well-designed studies that account for variations in dosage, gestational age, renal clearance, transplacental transfer efficiency and potential counter-transport mechanisms, which are as yet not well understood[82]. Metformin in pregnancy is currently classified as a 'category B' drug by the FDA[84], as no animal or human fetal toxicity or teratogenicity has been reported so far on the basis of clinical open-label, randomized or non-randomized trials[85]. Despite its apparent safety in pregnancy, some observational studies and clinical trials have produced conflicting results regarding longer-term safety, with some follow-up studies indicating potential adverse child health outcomes from maternal metformin use (mainly in relation to

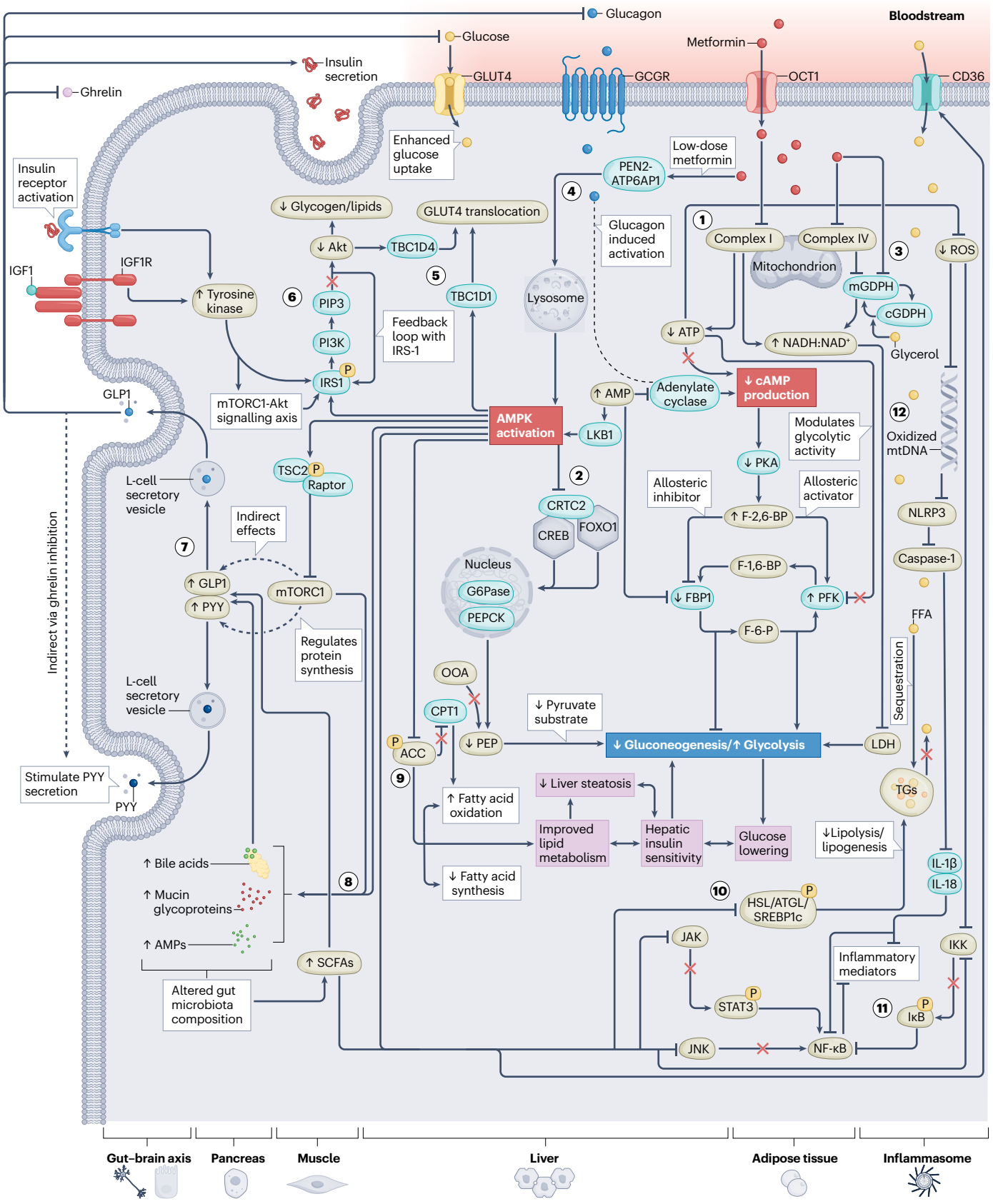
Glucagon
Bloodstream
Glucose
Metformin
Insulin secretion
GLUT4
GCGR
OCT1
CD36
Ghrelin
Enhanced glucose uptake
Low-dose metformin
PEN2-ATP6AP1
Insulin receptor activation
↓ Glycogen/lipids
GLUT4 translocation
Glucagon induced activation
Complex I
Complex IV
↓ ROS
Mitochondrion
mGDPH
cGDPH
Glycerol
IGF1
IGF1R
↑ Tyrosine kinase
↓ Akt
TBC1D4
TBC1D1
Lysosome
PIP3
PI3K
Feedback loop with IRS-1
IRS1
↓ ATP
↑ NADH:NAD+
GLP1
mTORC1-Akt signalling axis
↑ AMP
Adenylate cyclase
↓ cAMP production
AMPK activation
LKB1
Modulates glycolytic activity
Oxidized mtDNA
↓ PKA
TSC2
Raptor
Allosteric inhibitor
Allosteric activator
NLRP3
L-cell secretory vesicle
CRTC2
CREB
FOXO1
↑ F-2,6-BP
Caspase-1
Indirect effects
Nucleus
F-1,6-BP
↑ GLP1
↑ PYY
mTORC1
G6Pase
PEPCK
↓ FBP1
↑ PFK
FFA
Regulates protein synthesis
F-6-P
Indirect via ghrelin inhibition
OOA
Sequestration
CPT1
↓ Pyruvate substrate
L-cell secretory vesicle
ACC
↓ PEP
↓ Gluconeogenesis/↑ Glycolysis
LDH
Stimulate PYY secretion
PYY
↑ Fatty acid oxidation
↓ Liver steatosis
TGs
Improved lipid metabolism
Hepatic insulin sensitivity
Glucose lowering
↓Lipolysis/ lipogenesis
↑ Bile acids
↓ Fatty acid synthesis
IL-1β
IL-18
↑ Mucin glycoproteins
HSL/ATGL/ SREBP1c
↑ AMPs
JAK
IKK
Inflammatory mediators
↑ SCFAs
STAT3
IκB
Altered gut microbiota composition
JNK
NF-κB
Gut–brain axis
Pancreas
Muscle
Liver
Adipose tissue
Inflammasome

Fig. 2 | Complex mechanisms of metformin in cellular metabolism. (1) Metformin mildly inhibits mitochondrial respiratory chain complex I, increasing the cellular NADH:NAD^+ ratio and reducing ATP with a concomitant rise in AMP. Elevated AMP inhibits adenylate cyclase, reducing ATP-to-cAMP conversion upon glucagon receptor stimulation, thereby reducing PKA activation. Diminished PKA increases F2,6BP, an allosteric inhibitor and activator of FBP1 and PFK, respectively, altering enzymatic activity to suppress gluconeogenesis and stimulate glycolysis. (2) The increased AMP:ATP ratio enhances LKB1-mediated AMPK activity, leading to phosphorylation and nuclear exclusion of transcription factors (CREB and FOXO1) via CRTC2. This prevents activation of gluconeogenic genes *PEPCK* (also known as *PCK2*) and G6Pase genes, reducing substrate availability for gluconeogenesis. (3) Metformin is thought to inhibit mGPDH directly in a redox-independent manner and indirectly via inhibiting complex IV. This reduces glycerol-phosphate shuttle activity and increases the NADH:NAD^+ ratio, which inhibits LDH, decreasing lactate-derived pyruvate substrate availability for gluconeogenesis. (4) A novel pathway suggests that, at low but clinically relevant doses, metformin binds PEN2, initiating a signalling route that interacts with the lysosomal glucose-sensing pathway via ATP6AP1 to activate AMPK. (5) In skeletal muscle, metformin-activated AMPK enhances glucose uptake by promoting GLUT4 translocation to the cell membrane, either directly via effects on TBC1D1 or indirectly through modulation of the insulin signalling pathway (PI3K–Akt–IRS-1). (6) Activated AMPK promotes IRS1 phosphorylation, inhibiting downstream molecules PI3K and PIP3 and reducing Akt activation. Akt can also modulate IRS1, creating a feedback loop. Diminished Akt affects multiple downstream targets (for example, CREB, FOXO1, NF-κB and mTORC1). (7) AMPK inhibits mTORC1 via TSC2 phosphorylation, promoting autophagy. This indirectly affects the gut hormones GLP1 and PYY, which mediate the gut–brain axis to modulate glucose homeostasis. The hunger hormone ghrelin suppresses PYY, thus suppression of ghrelin by GLP1 might indirectly stimulate PYY. (8) AMPK upregulates gut antimicrobial peptides, mucin glycoproteins and bile acids, which modulate gut hormones and microbiota composition and enhance SCFAs to support various metabolic functions. (9) AMPK activation inhibits ACC, reducing de novo lipogenesis and promoting fatty acid oxidation via relieving inhibition of CPT1. (10) AMPK regulates lipolysis by phosphorylating ATGL and HSL and inhibiting hydrolysis of triglycerides to glycerol and fatty acids and phosphorylates SREBP1c to inhibit lipogenesis. Translocation of CD36 by activated AMPK might also support fatty acid uptake and sequestration. (11) AMPK activation inhibits NF-κB signalling via preventing IκB phosphorylation and nuclear translocation of NF-κB dimers. Inhibition of NF-κB, via disruption of JNK and JAK–STAT signalling pathways and AMPK-independent pathways via ROS, has been proposed. (12) Reduced ATP from complex I inhibition by metformin can directly or indirectly (via reduced ROS) lower cytosolic mtDNA (a potent NLRP3 inflammasome ligand) via a novel AMPK–NF-κB independent pathway. Decreased NLRP3 and caspase-1 inhibit proteolytic IL-1β and IL-18 activation and disrupt differentiation and activation of immune cells and downstream inflammatory pathways. The organs illustrated are the primary (but not exclusive) sites for the actions of metformin as depicted. ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; AMP, antimicrobial peptide; ATGL, adipose triglyceride lipase; ATP6AP1, ATPase H^+ transporting accessory protein 1; CPT1, carnitine palmitoyltransferase 1; CREB, cAMP response element-binding protein; CRTC2, CREB-regulated transcription co-activator 2; CXCL, chemokine (C-X-C motif) ligand; F-1,6-BP, fructose-1,6-bisphosphate; F-2,6-BP, fructose-2,6-bisphosphate; F-6-P, fructose-6-phosphate; FBP1, fructose-1,6-bisphosphatase; FFA, free fatty acid; FOXO1, forkhead box protein O1; G6Pase, glucose-6-phosphatase; GCGR, G protein-coupled receptor; GLP1, glucagon-like peptide 1; GLUT4, glucose transporter type 4; HSL, hormone-sensitive lipase; IGF1, insulin-like growth factor 1; IκB, inhibitor of κB; IKK, IκB kinase; IRS1, insulin receptor substrate 1; JAK, Janus kinase; JNK, Jun N-terminal kinase; LDH, lactate dehydrogenase; LKB1, liver kinase B1; mGPDH or cGDPH, mitochondrial or cytosolic glycerol-3-phosphate dehydrogenase; mTORC1, mechanistic target of rapamycin complex 1; NAD or $NADH^+$, nicotinamide adenine dinucleotide + hydrogen; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor protein 3; OOA, oxaloacetate; PEP, phosphoenolpyruvate; PEPCK, phosphoenolpyruvate carboxykinase; PEN2, presenilin enhancer 2; PFK, phosphofructokinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKA, protein kinase A; PYY, peptide tyrosine–tyrosine; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SREBP1c, sterol regulatory element-binding protein 1c; STAT, signal transducer and activator of transcription; TBC1D1 or TBC1D4, TBC1 domain family member 1 or 4; TG, triglyceride; TSC2, tuberous sclerosis complex 2.

obesity)[86,87]. However, these data are inconclusive. Inconsistencies in the literature are complicated by heterogeneity in study designs, participant risk profiles and treatment regimens, as well as variable methodological quality, with many studies affected by poor compliance, high attrition and lack of control for extraneous variables (diet, lifestyle and so on). With the rising prevalence, high health and cost burden, continuing controversies and escalating research on metformin treatment in GDM, a synthesis of the literature is pertinent to improve understanding of the current evidence base and facilitate advancements in this field.

Metformin efficacy in GDM

Retrospective observational studies

Several retrospective cohort and case–control studies have examined the effects of metformin on maternal and neonatal outcomes in women with GDM (Supplementary Table 1). In 2008, Tertti et al.[88] conducted the first retrospective case–control study, comparing metformin with insulin or diet alone in the treatment of 173 women with GDM. During the first 2 h postpartum, the incidence of neonatal hypoglycaemia was significantly lower in the metformin-treated group than in the insulin-treated group ($P = 0.03$)[88]. Approximately 18% of the women on metformin required supplemental insulin in this study. A larger retrospective cohort study of 592 women in the UK[89] reported a reduced incidence of macrosomia and large-for-gestational age (LGA) infants after treatment with metformin compared with lifestyle modification. This finding was corroborated by an Australian cohort study[90] ($n = 63$), in which the metformin group was less likely to have LGA infants than those receiving metformin plus insulin, but this effect was attenuated after adjustment for maternal BMI[90]. In another Australian case–control study[91] ($n = 2,505$), metformin treatment was associated with lower birthweight and shorter gestational age compared with diet treatment. The finding of shorter gestation (and the probably related lower birthweight) could be associated with earlier obstetric intervention in women receiving metformin versus diet intervention rather than the pharmacological effect of metformin on neonatal development, although this could not be determined given the retrospective nature of the data[91]. Similarly, Bashir et al.[92] reported that in a cohort study of 801 women with GDM in Qatar, metformin was associated with a lower risk of macrosomia, gestational weight gain and neonatal hypoglycaemia than lifestyle modification (diet and exercise). However, 35% of participants required supplemental insulin to achieve glucose targets. Reasons for insulin requirement could not be determined owing to missing data, including the dose of metformin administered (which might have been too low to adequately control glucose) and the gestational age at which treatment commenced (which might have been too late in gestation after glucose intolerance was well established).

A large Swedish retrospective cohort study[93] of 2,345 women (2,476 pregnancies) reported that metformin monotherapy was associated with marginally lower rates of LGA infants

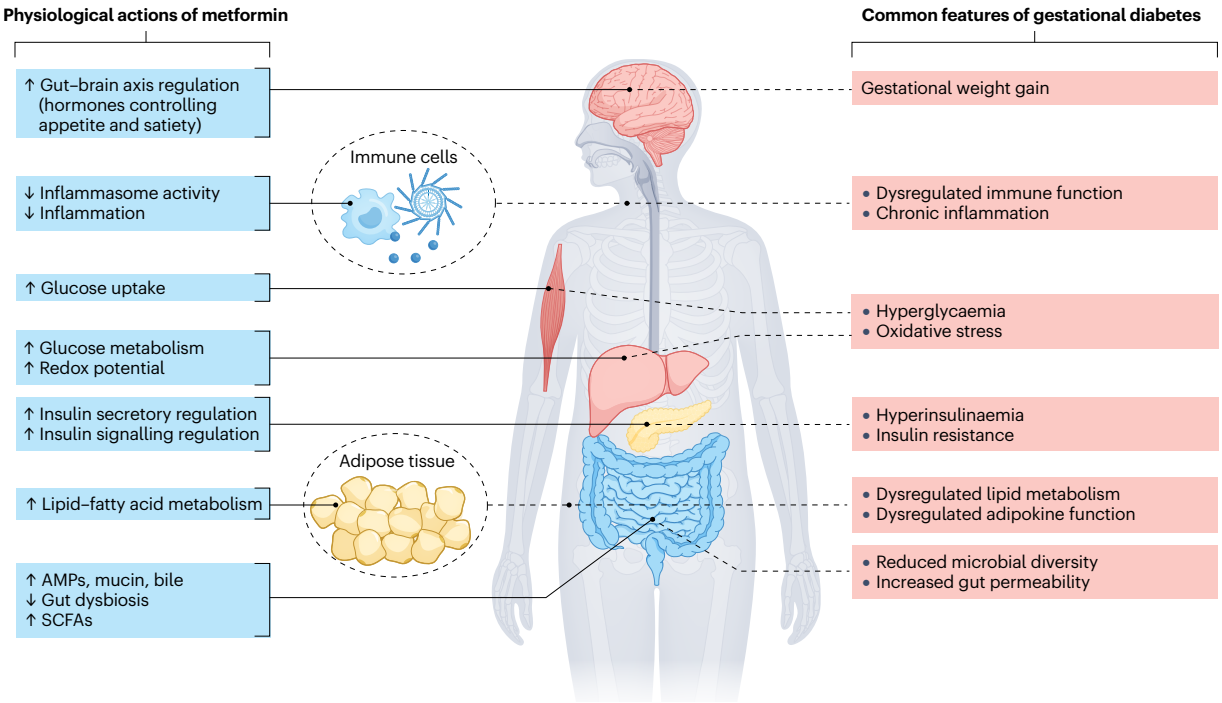

Fig. 3 | Actions of metformin target key features of gestational diabetes mellitus. Metformin exerts pleiotropic physiological actions at various organs and tissue sites (left). These actions target key mechanisms underpinning common features of gestational diabetes mellitus (right). AMP, antimicrobial peptide; SCFA, short-chain fatty acid.

(and correspondingly lower numbers of Caesarean sections) compared with insulin treatment, but similar LGA outcomes were observed with metformin plus insulin versus insulin alone[93]. In the largest population-based retrospective cohort study to date, which assessed pharmaceutical claims from 7,268 women in New Zealand[94], those who initiated metformin had lower rates of LGA, neonatal hypoglycaemia and planned elective Caesarean section than those who initiated insulin treatment. Methodological limitations were notable, including the use of national maternity collection data alone to identify pregnancies, which under-represents the New Zealand obstetric population, especially for certain outcomes such as early terminations, pregnancy losses and stillbirths[94]. More importantly, using pharmaceutical claims data only ascertained metformin or insulin 'initiation', which does not account for the inherently varied baseline risk profiles of these groups, nor does it adequately describe adherence to these medications, both of which are key factors for accurately determining treatment efficacy.

Conversely, retrospective cohort studies by Vanlalhruaii et al.[95] in India and Khin et al.[96] in the UK found no differences in maternal or neonatal outcomes with metformin versus insulin use in 540 and 215 women, respectively. Although not statistically significant, both studies reported a higher occurrence of preterm birth in women using metformin compared with insulin. However, it should be noted that 47.3% (ref. 95) and 55.8% (ref. 96) of women in these studies required supplemental insulin. It is possible that the preterm births might be related to failure of metformin to adequately manage hyperglycaemia in these women or potential adverse effects of metformin, or both. In a cohort study of 740 women diagnosed with GDM, no differences in Caesarean section delivery rates or maternal outcomes with metformin versus diet and/or insulin treatment were observed, but a 15% metformin monotherapy failure rate was reported[97]. Poor glycaemic control by metformin was also suggested in a case–control study[98] of 2,891 women recruited from 25 Portuguese hospitals, whereby metformin was ineffective in achieving adequate glycaemic control in 23.7% of women with GDM. High maternal age, high pre-pregnancy BMI and early introduction of metformin (all of which indicate more severe GDM) were independent predictors for the need for supplemental insulin[98].

Owing to the retrospective nature of these studies and the inherent methodological limitations therein, causal inferences cannot be established, and results should be interpreted with caution. Some retrospective studies suggest that metformin might be a safe and effective treatment for certain women with GDM, yet there are many instances in which metformin failure prompted the use of supplemental insulin to achieve glucose targets. Although definitive conclusions cannot be drawn from these studies, they underscore the importance of identifying key risk factors for metformin failure to facilitate risk prediction and early intervention for those who are likely to require further treatment.

Prospective observational studies

Several prospective studies have examined the relative safety and efficacy of metformin use in pregnancy (Supplementary Table 1). In 2009, a case–control study by Balani et al.[99] in the UK and an observational study by Rai et al.[100] in India investigated 200 and 60 women, respectively, receiving metformin versus insulin[99,100]. Metformin attenuated gestational weight gain and improved several neonatal outcomes including hypoglycaemia and admissions to neonatal intensive care

units (NICUs) compared with insulin. In 2012, Balani et al.[101] conducted another case–control study in the UK, examining 499 women treated with metformin versus diet intervention. This more recent study identified a decreased proportion of LGA and small-for-gestational-age (SGA) infants, but also showed an increased rate of induced labour and elective Caesarean sections in the metformin group compared with diet treatment[101]. This finding is not surprising, given that the study was not randomized; hence, the women prescribed metformin would have worse baseline risk profiles, including high BMI and high levels of glycosylated haemoglobin (HbA1c) and poorly controlled glucose[101]. A prospective non-randomized study[102,103] in which women with GDM inadequately controlled by diet only were given metformin suggested that glycaemic control can be achieved with metformin, with no adverse effects. However, efficacy could not be established, as no comparisons were made with the 'diet' group. In the largest prospective observational study to date[104] comprising 1,269 women in New Zealand, metformin use was associated with similar or lower incidence compared with diet, and lower incidence compared with insulin, for the outcomes of preterm birth (12.5% metformin versus 12.1% diet versus 19.2% insulin), LGA (12.5% metformin versus 12.4% diet versus 18.5% insulin), NICU admissions (12.7% metformin versus 14.0% diet versus 18.7% insulin) and need for neonatal intravenous dextrose (5.1% metformin versus 7.4% diet versus 11.1% insulin). Similarly, studies in Europe[105] and Qatar[106] have reported that metformin therapy improved maternal glycaemic control, neonatal birthweight and LGA compared with diet and/or insulin.

By contrast, a clinical audit and a cohort study in Australia[107,108] found no differences in any pregnancy outcomes among metformin, insulin or diet, probably owing to the small sample sizes and inadequate statistical power ($n = 71$ (ref. 107) and $n = 151$ (ref. 108)). In addition to these methodological limitations, discrepancies between these two studies and other prospective studies might be due to varying baseline risk profiles of study participants. Indeed, Brzozowska et al.[108] reported that higher fasting blood glucose (FBG) during the oral glucose tolerance test might be a key indicator of women with GDM who require pharmacological intervention (beyond diet) for effective treatment. These points emphasize the importance of further investigation into the association between pharmacological interventions and obstetric outcomes in randomized controlled trials and the need to use larger sample sizes to enable stratification by risk factors such as age, BMI and FBG levels.

Across all these prospective studies, the need for supplemental insulin was relatively low, ranging from 1.6% to 10.5%, with two studies reporting higher proportions of women (33.3% and 36%) requiring insulin to meet glycaemic targets[106,107]. Although the exact predictors of the need for supplemental insulin are unclear, Souza et al.[109] conducted a case–control study of 475 women and reported that women with obesity had an increased likelihood of needing additional treatment with insulin, whereas primiparity and an FBG <90 mg/dl during an oral glucose tolerance test were negative predictors for the need for insulin.

In a prospective pharmacodynamics study assessing the relative efficacy of metformin[110], glyburide and their combination in GDM, metformin monotherapy was more effective in improving insulin sensitivity than glyburide (121%) and combination therapy (81%). The authors proposed that a stepwise approach might be beneficial in the management of GDM, whereby metformin monotherapy is used first to maximize insulin sensitivity, followed by glyburide to enhance β-cell responsivity[110].

Overall, prospective data indicate that metformin might be an effective alternative to insulin in women with GDM, but valid conclusions are difficult to reach owing to substantial heterogeneity in participant (baseline risk profiles, FBG levels, ethnic composition and so on) and study (diagnostic criteria for GDM and regimen of metformin administration) characteristics. Given the lack of placebo-controlled groups in these studies, a placebo effect might also be at play, with participants altering health behaviours and improving dietary adherence owing to perceived severity and/or risk following drug prescription. Furthermore, given the observational nature of these studies, adequate consideration for extraneous variables (including diet and comorbidities) is not always possible, and groups are often poorly matched for key variables affecting pregnancy outcomes including pre-pregnancy or early pregnancy BMI and glycaemic control at baseline. For these and other reasons, properly designed randomized controlled trials are often more useful in establishing drug efficacy, particularly in the heterogeneous contexts of pregnancy and GDM.

Randomized controlled trials

A series of open-label RCTs have been published comparing the efficacy and safety of insulin and metformin in pregnancy (Supplementary Table 1). In 2003, a small study by Hague et al.[111] suggested no differences in fetal and perinatal outcomes in GDM-complicated pregnancies treated with metformin versus insulin. A number of trials[112–116] have since supported some benefits of metformin over insulin, primarily for reducing gestational weight gain, in addition to lower costs and better compliance[114]. In the early landmark Metformin in Gestational diabetes (MiG) trial, comprising 751 pregnant women with GDM, Rowan et al.[117] reported reduced gestational weight gain and a patient preference for metformin over insulin, although no difference in the primary outcome was observed (which was a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-min Apgar score <7 and prematurity). Notably, 46.3% of the women in the metformin group required supplemental insulin[117], making it difficult to isolate the effects of metformin on these outcomes.

In terms of glycaemic control, various trials have demonstrated that metformin is a safe and comparable treatment to insulin in pregnant women with GDM[112,118–121]. In some studies, women allocated to the metformin group achieved lower postprandial glucose levels[112] and had lower FBG levels during the first and last 2 weeks of treatment[120] than those in the insulin group, whereas other studies indicated no difference in FBG, 2-h postprandial blood glucose[118] or HbA1c levels[121]. However, these studies all had sample sizes of ≤100 women. Slightly larger trials (ranging from 137 to 286 women)[113,115,122–128] found that metformin was comparable to insulin for managing GDM without added adverse outcomes, and with some favourable outcomes compared with insulin, including reducing postprandial glucose levels[112] and frequency of maternal hypoglycaemic episodes[126], as well as increasing peripheral insulin sensitivity and plasma insulin levels[124]. Huhtala et al.[129] also showed a greater increase in levels of some amino acids (alanine and isoleucine) in GDM-complicated pregnancies treated with metformin compared with insulin. This indicates the ability of metformin to depress gluconeogenesis in the liver and improve metabolic health by reducing conversion of alanine to pyruvate and limiting the breakdown of isoleucine to gluconeogenic or ketogenic intermediates, such as acetyl-CoA. Notably, the effects reported in these RCTs cannot be attributed purely to metformin, particularly given that many women

in these trials required supplemental insulin treatment, which is probably masking the true effects of metformin, if any.

A double-blind placebo-controlled RCT by Dunne et al.[130] included 510 women with GDM in Ireland and found that metformin was not superior to placebo for the primary composite outcome of insulin initiation or FBG of ≥5.1 mmol/l at 32 or 38 weeks gestation. However, improved secondary outcomes were reported with metformin, including time to insulin initiation, mean FBG at 32 and 38 weeks, results of capillary blood glucose self-monitoring and gestational weight gain. Metformin also resulted in smaller neonates (lower birthweight and crown–heel length and fewer LGA or macrosomic infants), with no differences in adverse neonatal outcomes compared with placebo (including, for example, NICU admission, respiratory distress, jaundice or hypoglycaemia). The generalizability of these findings is limited by the lack of ethnic diversity in the study population (80% White European) and the tight glucose targets for insulin initiation utilized in this study (two or more home readings >5.1 and >7 mmol/l for FBG and 1-h postprandial glucose, respectively)[130].

In addition to insulin or placebo, metformin has also been compared with glyburide. In a study of 104 women diagnosed with GDM, Nachum et al.[131] reported comparable glucose-lowering effects for metformin and glyburide and noted a few additional benefits of metformin, including reduced gestational weight gain, reduced rates of pregnancy-induced hypertension, improved postprandial blood glucose levels and less requirement for supplemental insulin (4% versus 17% required insulin in metformin versus glyburide groups, respectively). Conversely, Moore et al.[132] (n = 149) reported that the failure rate for achieving glycaemic control was twice as high in the metformin group (34.7% requiring insulin) than in the glyburide group (16% requiring insulin), with the former also having higher rates of emergency Caesarean section. These results should be interpreted in the light of the relatively small sample sizes and the possible influence of ethnic variation in individual responses to metformin (given that 86% of participants were Hispanic in the study by Moore et al.[132]) — an aspect that warrants consideration in future metformin trials.

Despite some trials indicating similar outcomes for metformin compared with insulin or placebo, with some outcomes favouring metformin (for example, weight gain and neonatal hypoglycaemia), long-term data on the use of metformin in pregnancy are limited, with some adverse outcomes suggested. Follow-up of the MiG trial demonstrated increased bicep and subscapular skin fold thickness and upper arm circumference at both 2 and 7–9 years of age[87,133]. Metformin-exposed children were also larger at 9 years of age than infants exposed to insulin therapy in utero[133]. Potential limitations to these findings were noted, including high attrition of the original study participants, particularly for some ethnic groups. Subgroups in these follow-up analyses were also not well matched in key variables, with the metformin group having higher maternal glycaemia and infant birthweight than the insulin group[87,133]. A similar follow-up study by Ijäs et al.[86] found that infants prenatally exposed to metformin were heavier at 12 months and heavier and taller at 18 months of age than their insulin-exposed counterparts, but with no differences in ponderal index or developmental skills. No differences were noted in neurodevelopmental outcomes at 2-year-old for children born to mothers with GDM treated with metformin versus insulin[134]. Given the paucity of data, the effect of intrauterine metformin exposure on offspring growth and future obesity or metabolic risk cannot be determined from the available evidence.

Systematic reviews and meta-analyses

Several systematic reviews and meta-analyses have explored metformin use in GDM (Supplementary Table 1). Most of these (with many overlapping studies) report that metformin is equally[135–141], if not more[142–144], efficacious and safe in comparison to insulin and other oral hypoglycaemic agents. Partly in line with results from individual RCTs, potential benefits of metformin include lower rates of neonatal hypoglycaemia[136,139,145–152], emergency Caesarean section[136,140], hypertensive disorders in pregnancy[137,139,143,147,151–154] and NICU admissions[137,151,152,155,156] as well as less gestational weight gain compared with insulin[143,145–147,149,151–153,157]. Nausea, increased bowel movements, epigastralgia and constipation are the most commonly reported adverse effects associated with metformin treatment[112,139]. Some meta-analyses have also reported a slightly increased risk of preterm birth or lower gestational age at birth associated with metformin (by 0.16 weeks or 1.12 days)[136,145,146], whereas others report a reduced incidence with metformin (9% versus 16%)[139] or no effect[147] compared with insulin. Other studies have reported lower rates of LGA and macrosomia with metformin than with insulin[147,151,157] or glyburide[148]. Concerns over growth restriction or SGA risks with metformin have not generally been supported by these pooled analyses, with most showing no differences in rates of SGA with metformin compared with insulin[147,158]. The use of metformin combined with insulin was, however, associated with a more pronounced reduction in average birthweight and gestational weight gain than insulin treatment alone[158].

Regarding longer-term outcomes, pooled analyses demonstrate the paucity of follow-up data for maternal and fetal outcomes[144,156]. Although some increases in offspring weight beyond the neonatal period have been documented (that is, accelerated postnatal catch-up growth)[150,153,157,159], evidence of identifiable differences in body composition or metabolic parameters in the long term is weak[160,161]. The clinical relevance of these findings therefore remains unknown. Moreover, given the considerable heterogeneity between existing studies, the grouping of aggregate and often inharmonious data within meta-analyses remains problematic and probably contributes to these disparate results. As such, more innovative analytical approaches are needed to account for variations in individual participant (such as BMI, ethnicity and baseline FBG) and treatment (diagnostic criteria, timing for initiation of treatment and duration of follow-up) characteristics. Examining the potential influence of these factors is important to understand and optimize the efficacy of metformin treatment for improving glycaemic control and pregnancy outcomes in GDM.

Limitations and future directions

Metformin has complex multiorgan effects that, at a physiological level, would suggest clinical benefits for the treatment of GDM. In addition, as reviewed here, there is no evidence that metformin treatment during pregnancy has adverse effects on maternal or offspring health, aside from gastrointestinal discomfort[139] and some suggested adverse long-term child outcomes that cannot be directly attributed to intrauterine metformin exposure. However, the efficacy and safety of metformin compared with insulin or other oral hypoglycaemic agents cannot be definitively established owing to the limited number of trials conducted and divergent findings, with heterogeneous diagnostic criteria, treatment targets, populations and outcomes, as well as a number of methodological factors limiting interpretation.

First, many of the current findings are based on data gathered from observational studies, which can lead to potential under-estimation or

over-estimation of treatment effects. These studies are also subject to bias and confounding owing to interindividual variations in several key factors, including baseline risk profiles and severity of GDM, concurrent maternal well-being and/or comorbidity status, as well as antenatal and postnatal factors and duration of follow-up. For instance, animal-based studies have demonstrated that maternal diet was a primary factor influencing the effect of metformin during pregnancy on offspring glucose tolerance and adiposity in the long term[89,90], but diet is seldom incorporated in these studies.

Second, study-related factors including unblinded treatment and variable metformin regimens (low doses or poor compliance and late commencement) can mask or obscure the reported effect of metformin on pregnancy outcomes. Variations in diagnostic criteria, intervention doses, durations and timing, treatment targets and differences in patient characteristics further complicate our understanding of the precise benefits of metformin (or lack thereof) in this context. This issue becomes even more challenging when considering the use of supplemental insulin to achieve glycaemic control, as is the case in many of the existing RCTs. The exact causes for metformin failure and the need for insulin thus remain poorly understood and warrant further study, particularly given the multifaceted antidiabetic actions of metformin and its known benefits for treating T2DM. One theory suggests that patients with GDM exhibit a greater degree of insulin resistance than patients with T2DM, exacerbated by placental hormones, which cannot be overcome by metformin alone. By inducing insulin resistance[4], counter-regulatory placental hormones such as human placental lactogen and placental growth hormone might neutralize the insulin sensitizing effects of metformin as pregnancy progresses. Metformin pharmacokinetics also differ in the pregnant state (probably owing to increased plasma volume and renal clearance)[17]; hence, standard therapeutic doses might be unable to sufficiently counteract the increased hepatic glucose production that occurs in pregnancy to support fetal energy demands.

Another issue pertains to the heterogeneous pathology underlying GDM, in which the central dysfunction might relate to varying degrees of insulin resistance or insulin secretory dysfunction, or a combination of the two. Monotherapies that treat only one facet of GDM might not be suitable, such as using metformin (which treats insulin resistance) in women with GDM resulting from β-cell dysfunction. The physiological complexity of GDM, coupled with study design limitations, has collectively hindered our ability to determine whether there are possible benefits for metformin and for whom. Therefore, a systematic approach is needed to identify which subgroups of women, if any, would benefit from metformin monotherapy or adjunctive therapy versus those who are susceptible to metformin failure. One such approach would be via individual patient data (IPD) meta-analysis of existing RCT data, which is less costly than a new RCT, and would provide a large, diverse and adequately powered dataset to establish metformin efficacy and identify key predictors of individual responses to metformin. The Metformin in Pregnancy Study (MiPS) international network[162] is currently underway to address these critical questions and has thus far collated IPD from 22 RCTs, comprising ~6,000 women with various metabolic disorders including GDM.

Finally, the lack of high-quality long-term data is a central issue surrounding the use of metformin in pregnancy, with both benefits and harms proposed in relation to fetal health. By reducing hepatic gluconeogenesis and insulin resistance, metformin could theoretically reduce intrauterine metabolic stress and preserve offspring fetal β-cell function, thus reducing future T2DM risk[163]. However, metformin has also been shown to impair insulin secretion in human and rodent islets under normoglycaemic conditions, leading to toxicity, suppressed proliferation and apoptosis of β-cells in the absence of metabolic stress[164,165]. This can reduce fetal β-cell mass and diminish the ability of β-cells to withstand lifelong glucose or nutrient challenges, translating to earlier development of β-cell dysfunction and T2DM[82]. Metformin also reduces androgen levels, which can bring about favourable intrauterine conditions and reduced risk of metabolic and reproductive disorders caused by excess androgen exposure, particularly in women with hyperinsulinaemic and hyperandrogenic conditions such as PCOS[82]. However, in patients without PCOS or with non-hyperandrogenic phenotypes, prenatal exposure to metformin might disrupt hormonal balance and ovarian steroidogenesis, affecting reproductive development in female offspring[82]. In male offspring, metformin exposure in utero has been linked to decreased testosterone secretion and reduced Sertoli cell numbers[166], potentially leading to subfertility or increased risk of testicular cancer in later life, although the latter effects have not been demonstrated[82]. In non-pregnant adults, metformin has been associated with a lower risk of cancer-related death than insulin or sulfonylureas[167], thought to occur via reducing AMPK-activated regulation of gene expression and mTOR protein synthesis and by triggering low-energy state responses[168,169]. Although these antineoplastic effects are beneficial in cancer, cell growth and high energy demands are necessary for embryogenesis and organogenesis. Restricting these processes by metformin might interfere with fetal cell growth and differentiation, with lifelong health consequences[82]. The antifolate action of metformin can also lead to methionine deprivation and decreased synthesis of purines and pyrimidines, restricting nutrients and further inhibiting cell growth[170]. According to the developmental origin of health and diseases hypothesis[171], such adverse intrauterine exposures might lead to disrupted DNA methylation and epigenetic programming and thus to chronic disorders later in life. However, evidence to this effect is lacking, and optimal therapeutic ranges for metformin that can minimize fetal harm while extracting maximal benefits have not been established. To better understand the effect of intrauterine metformin exposure on long-term child health, long-term RCT data are needed with sufficient sample sizes to account for attrition and adjust for important confounders. These studies are necessary to weigh the long-term impact of gestational hyperglycaemia against possible treatment effects that might not be apparent until late childhood or early adolescence. As with other outcomes, these long-term end points are currently being investigated in the MiPS network[162], using an IPD meta-analysis of follow-up data from existing RCTs.

Conclusions

In summary, metformin is an attractive option for GDM treatment given its low cost and ease of administration, but current evidence has not demonstrated whether it is adequately effective in this context and for whom. Given the large number of existing RCTs, the use of IPD meta-analysis to bring together these datasets is a key next step to progressing this field of research. To this end, the MiPS network[162] is an important initiative that will address critical gaps regarding metformin efficacy and identify the key pharmaco-epidemiological factors that govern the benefits and/or potential harms of its use in pregnancy.

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Competing interests
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Review criteria We searched electronic databases including PubMed, Scopus, Science Direct, Google Scholar and the Cochrane Library, to identify studies examining the use of metformin in pregnant women with GDM. The search was not systematic and is not intended to introduce new data or conclusions. Rather, the aim was to provide a broad overview of the state of the evidence and identify key gaps to inform future research efforts. Search terms included 'gestational diabetes', 'metformin', 'safety', 'efficacy' or 'effect' and 'pregnant'. Original studies of any design, as well as systematic reviews and meta-analyses, examining the use of metformin in pregnant women with GDM were included. Studies without original data or that were not available in English were excluded, as were studies in women without GDM at study entry, women who did not receive metformin during pregnancy and women examined in the preconception or postpartum periods.

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